

REMARKS

In the Office Action, claims 235-244, 327, 340, 353 and 366 were rejected under 35 USC 112, first paragraph as lacking written description. Claims 298, 299, 301-309, 330, 343, 356 and 369 were rejected under 35 USC 112, first paragraph as lacking written description. Claims 300, 310-318, 331, 344, 357 and 370 were rejected under 35 USC 112, first paragraph as lacking written description. Claims 225-234, 265-274, 319-322, 326, 329, 332-335, 339, 342, 345-348, 352, 355, 358-361, 365, 368 and 371-372 were rejected under 35 USC 112, first paragraph as lacking enablement. Claims 298, 299, 301-309, 330, 343, 356 and 369 were rejected under 35 USC 112, second paragraph as indefinite. Claims 323, 324, 336, 337, 349, 350, 362, 363 and 373 were found allowable but for dependence on a rejected base claim. Claims 215-224, 255-264, 325, 328, 338, 341, 351, 354, 364 and 367 were allowed.

Request for Telephonic Interview Prior to First Action

In accordance with MPEP Sections 706.07(b), 713.01 and 713.02 and 37 CFR 1.133(a)(2), Applicant hereby requests an interview prior to any subsequent Office Action. As this is a continuing application, such an interview is proper. The undersigned may be reached at 858-228-7829.

Written Description

MPEP 2163 (III)(A) sets forth the procedural standard for determining the adequacy of the description of a claimed invention during prosecution:

A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. See, e.g., *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). The examiner, therefore, must have a reasonable basis to challenge the adequacy of the written description. The examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *Wertheim*, 541 F.2d at 263, 191 USPQ at 97.

The written description standard simply requires that one of skill can recognize the identity of the claimed subject matter in the disclosure. No particular form of disclosure is required.

[T]he language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. ... The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 296 F.3d 1316, 1328, 1329 (Fed. Cir. 2002), internal citations omitted.

Functional language is permitted in the claims, and functional descriptions of genetic material can satisfy the written description requirement. *Id. at 1324*.

The Federal Circuit has directly addressed the written description requirement for biological molecules:

Specifically, we hold, in accordance with our prior case law, that (1) examples are not necessary to support the adequacy of a written description (2) the written description standard may be met (as it is here) even where actual reduction to practice of an invention is absent; and (3) there is no *per se* rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure.

Falko-Gunter Falkner v. Inglis, 448 F.3d 1357, 1366, 79 U.S.P.Q.2d 1001, ____ (Fed. Cir. 2006) (emphasis added). That case involved claims to a virus comprising a mutant poxvirus lacking an essential gene. That specification did not describe the poxvirus genome (which was known in the art), nor what the essential genes were. It exemplified a mutant herpesvirus, and showed how to identify and mutate an essential gene of herpesvirus. It generally asserted the techniques could be followed with a poxvirus. This teaching was found to satisfy the written description requirement for claims to a vaccine comprising a mutant poxvirus lacking an essential gene.

Falko-Gunter thus explicitly rejects the bases for the written description rejections here.

The rejection of Claims 235-244, 327, 340, 353 and 366 as lacking written description

Claims 235-244, 327, 340, 353 and 366 were rejected under 35 USC 112, first paragraph, as lacking written description for reasons set forth in the Office Action of 11/14/2005. This rejection is traversed. The Office Action alleged that the lack of a representative species of a deletion mutant resulted in failure to adequately describe the invention. Office Action of 11/14/2005, page 2, fourth paragraph.

As set forth above, the Federal Circuit has explicitly rejected any requirement for examples or working embodiments to establish a written description of biological molecules. *Falko-Gunter.*

Applicants fully describe the structure of the Δ-6 desaturase protein and DNA, and demonstrate the function of the protein when expressed. The claims at issue recite the demonstrated function as a limitation. One of skill in the art can recognize deletion mutants of the fully disclosed SEQ ID NO's 1 and 2. Applicants have fully taught those sequences and demonstrated their (encoded) function. The process of making a deletion mutant is known in the art and is described in the specification. One following the teachings of the application and making a deletion mutant of the disclosed sequences will necessarily make functional deletion mutants thereof. That procedure would directly lead to the claimed invention.

The Office Action of July 18, 2006 concedes that Applicants are correct in describing these teachings of the application. Office Action, page 2, fifth paragraph. Nothing further is required to provide a written description of the invention.

Furthermore, the alignments described in this application (and shown in an incorporated parent application, *see* Fig. 5A of USPN 5,972,664, attached as Exhibit A) themselves show the presence of deletions in the aligned desaturases. This provides additional teaching to those of skill as to regions where deletions could be made and tested for activity.

As the only ground for the written description rejection of the deletion mutant claims are that no specific examples are shown, and the Federal Circuit has held that examples are not required, no valid grounds for this rejection have been stated.

The deletion mutants recited in the claims are described to one of skill as required by 35 USC 112, first paragraph. Withdrawal of the rejection is respectfully requested.

The rejections of Claims 298, 299, 301-309, 330, 343, 356 and 369

Claims 298, 299, 301-309, 330, 343, 356 and 369 were rejected under 35 USC 112, first paragraph as lacking written description. A written description rejection requires an analysis

of what one of skill in the art would have understood and why they would not have recognized the inventor was in possession of the invention:

[The examiner must e]stablish a *prima facie* case by providing reasons why a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed. A general allegation of "unpredictability in the art" is not a sufficient reason to support a rejection for lack of adequate written description.

Hyatt v. Dudas, --- F.3d ----, 2007 WL 1839700 (Fed. Cir. 2007).

As the Federal Circuit has recently made clear in *Falko-Gunter*, no examples or working embodiments are required for claims to meet the written description requirement. In that case, the differences between the disclosed examples and the claimed invention, involving a completely different family of viruses, were far more extensive than the modest alterations to fully disclosed sequences claimed here.

The examiner stated in the Office Action of 11/1/2005 that he could not find support for hybridization conditions in Examples 1 and 2 recited by Applicants. The examiner is requiring *ipsis verbis* support for a particular set of hybridization conditions, but as he is certainly aware, this is not required, and is explicitly rejected by the Federal Circuit as set forth at MPEP 2163:

What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d at 1384, 231 USPQ at 94. >See also *Capon v. Eshhar*, 418 F.3d 1349, 1357, 76 USPQ2d 1078, 1085 (Fed. Cir. 2005) ("The 'written description' requirement must be applied in the context of the particular invention and the state of the knowledge.... As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution.").< If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. See, e.g., *Vas-Cath*, 935 F.2d at 1563, 19 USPQ2d at 1116; *Martin v. Johnson*, 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972) (stating "the description need not be in *ipsis verbis* [i.e., "in the same words"] to be sufficient").

Determining hybridization conditions for a library was conventional and well known at the time of filing. The biotechnological field and the state of knowledge had advanced significantly by 1997. Applicants are not required to set forth the nuances of techniques that were well known at the time of the invention, in accordance with MPEP 2163. Furthermore, the examiner did not consider the other teachings of the specification cited by the Applicants.

Applicants have demonstrated where support can be found in Examples 1 and 2 and at page 5 lines 25-26, the paragraph bridging pages 17-18, and page 21 lines 7-13. Example 1 demonstrates the use of an initial PCR product which was sequenced and used as a probe to isolate corresponding cDNA clones from a *M. alpina* library. Example 2 describes the obtaining of a partial cDNA clone, Ma524, and states that a full-length cDNA was isolated. See the paragraph bridging pages 40-41. One of skill recognizes that the partial cDNA clone described in Example 2 would have been used as a probe to screen the full-length cDNA library described in Example 1 to obtain the full-length Δ6-desaturase sequence. Furthermore, the application describes elsewhere at multiple points the use of the disclosed sequences as probes to obtain desaturase sequences from recombinant libraries.

The examiner has made no attempt whatsoever at evaluating this support as is required, stating only that no support is found (11/14/05 Office Action, page 3, first paragraph). No evaluation has been provided of the support found at these citations, nor what these passages fairly teach one of skill. This noncharacterization of Applicants' teachings is not correct and does not meet the standard for establishing a written description rejection.

As the disclosure permits one of skill to recognize the claimed invention, the written description requirement has been met for claims 298, 299, 301-309, 330, 343, 356 and 369. Withdrawal of this rejection is respectfully requested.

The rejection of Claims 300, 310-318, 331, 344, 357 and 370 as lacking written description

Claims 300, 310-318, 331, 344, 357 and 370 were rejected under 35 USC 112, first paragraph as lacking written description. This rejection is traversed.

Claim 300 invokes the statutory provision of 35 USC 112, sixth paragraph.

As caselaw makes clear, disclosure in the specification of a single structure capable of performing the claimed function in a 112(6) claim renders a claim valid under section 112:

While the specification must contain structure linked to claimed means, this is not a high bar: “[a]ll one needs to do in order to obtain the benefit of [§ 112, ¶ 6] is to recite some structure corresponding to the means in the specification, as the statute states, so that one can readily ascertain what the claim means and comply with the particularity requirement of [§ 112,] ¶ 2.”

Atmel, 198 F.3d at 1382. Additionally, interpretation of what is disclosed in the specification must be made in light of the knowledge of one skilled in the art. *Id.* at 1380. Thus, in order for a means-plus-function claim to be valid under § 112, the corresponding structure of the limitation "must be disclosed in the written description in such a manner that one skilled in the art will know and understand what structure corresponds to the means limitation. Otherwise, one does not know what the claim means."

Biomedino, LLC v. Waters Technologies Corp., --- F.3d ----, 2007 WL 1732121 (C.A.Fed. 2007), 83 U.S.P.Q.2d 1118 (emphasis added, citations omitted), citing *Atmel Corp. v. Info. Storage Devices, Inc.*, 198 F.3d 1374 (Fed.Cir.1999) (holding invalid claims where no structure at all was taught in the application for the corresponding means).

The Office Action of 11/14/2005 acknowledges that a representative species from *M. alpina* having the claimed function is described. See page 3, third paragraph.

Where a corresponding structure is disclosed in the specification for a functional claim limitation under 112(6), the written description requirement is satisfied. MPEP 2181. Here, the Office Action admits a structure has been provided. The examples demonstrate the function for this sequence as recited in the claims, that of desaturating a fatty acid between carbons 6 and 7.

To the extent the rejection argues that additional examples are required, this is not a valid grounds of rejection for a 112(6) claim supported by a structure in the specification. See *Falko-Gunter Falkner v. Inglis*, discussed above.

As the specification describes a structure having the function recited in the claim, the written description requirement is satisfied for claim claim 300 and claims ultimately dependent thereon. Withdrawal of this rejection is respectfully requested.

The rejection of Claims 225-234, 265-274, 319-322, 326, 329, 332-335, 339, 342, 345-348, 352, 355, 358-361, 365, 368 and 371-372 as lacking enablement

Claims 225-234, 265-274, 319-322, 326, 329, 332-335, 339, 342, 345-348, 352, 355, 358-361, 365, 368 and 371-372 were rejected under 35 USC 112, first paragraph as lacking enablement. This rejection is traversed.

The disclosure fully teaches the protein and DNA sequences of the *M. alpina* Δ6-desaturase, as well as methods of manipulating sequences, and of testing for protein function. One of skill could further make hybridizing sequences and deletion mutants based on the disclosed sequences which would retain functional activity. One of skill in the art could make sequences having 60%, 80%, 90%, or 95% homology to the disclosed sequences by following the teachings in the application and applying those teachings to the disclosed sequences with ordinary experimentation. The Office Action admits that assays are disclosed for determining desaturase activity, and also admits that techniques were known for mutating sequences at the time of the invention. Applicants have further provided evidence of record that one of skill can functionally screen a large number of mutants in a given amount of time.

The Office Action alleges that the amount of experimentation needed to redesign the disclosed sequences is undue, but no factual evidence or findings have been provided as to how much experimentation would be needed to produce a single species having any of the recited claim limitations. No evidence has been provided as to how much experimentation by one of skill would be needed to produce a deletion mutant, a hybridizing sequence, or a homologous sequence meeting the claim limitations.

In the art of manipulating a fully disclosed sequence having a fully disclosed function, it is predictable that mutations can be made that will still retain function of the protein. Such experimentation is routine in the art of manipulating disclosed sequences. It also is routine to generate deletions and point mutations, which can have detectable homology, or whose coding sequences maintain ability to hybridize under conditions suitable for screening libraries. Furthermore, such claim scope is appropriate and is necessary to protect the inventors' contribution and avoid misappropriation of their invention by those who would seek to make minor alterations in the sequences they have taught.

Delta-six desaturases are taught by this and the incorporated parent applications to exhibit considerable flexibility in structure. The described alignments of these desaturases show low degrees of family homology, demonstrating that strict conservation of structure is not required for activity.

It is art recognized that numerous changes can be made in an enzyme from a family with low levels of sequence conservation while retaining enzymatic activity. Additionally, sequence alignments of related enzymes, as disclosed here, also provide information as to the location and types of mutations that can be made while maintaining activity.

Furthermore, sequences meeting the claim limitations for each class of claims could have been prepared by one of skill at the time of invention as detailed below.

Creation of homologous polypeptide sequences. At the time of the invention, one of skill in the art could have created a desaturase having 60% polypeptide homology to the *M. alpina* sequence using the disclosed sequences and delta-six desaturase sequences known at the time. Following the methods taught in the specification, including cassette mutagenesis, and using fragments from homologous but distantly related desaturases described in the application, one of skill could have created a delta-six desaturase meeting the recited homology requirements within at most a few months. Polypeptides with 70%, 80%, 90% or 95% homology could similarly have been created with less extensive cassette swapping between homologs.

A polypeptide having 60% homology could have been prepared by one of skill at the time of the invention by swapping the three desaturase histidine clusters with those from the previously known *Synechocystis*, *Spirulina* and *Borago officinalis* delta-six desaturases, as well as the transmembrane regions, the N-terminal cytochrome b5-like domain found in the borage and *Mortierella* sequences, and the C-terminal regions. The parent sequences all demonstrate the enzymatic activity recited in the claims.

Furthermore, although crystallographic data is not required, the cytochrome b5 crystallographic structure was in fact known at the time of the invention, contrary to assertions in the Office Action, and had been found to align with the b5-like domains of desaturase proteins, providing additional structural information useful in generating recombinants.

Creation of hybridizing and homologous nucleic acid sequences. It is known in the art that hybridization for probes of approximately 45 bp or longer requires ~70-80% sequence match for selective hybridization. Thus a probe would need at least this degree of homology to selectively hybridize under library screening conditions.

A nucleic acid having this level or the other recited degrees of homology could have been prepared from the disclosed *M. alpina* sequence quite simply by using the degeneracy of the genetic code without changing the encoded protein structure. This would require no more than three months, which is not undue experimentation in the field of reengineering sequences.

Thus a sequence embodying the outermost range of selective library hybridization conditions, demonstrating the full range of that claim scope, could be readily prepared from the disclosed sequence. So too could nucleic acid sequences having 60%, 70%, 80% or 90%, or 95% homology been achieved without changing the coding sequence, and would have taken no more than a few months. Due to the degenerate nature of the genetic code, all codons except for the relatively rare methionine and tryptophan could be changed in at least the third position, which would approach 67% homology. Codons for serine, leucine and arginine exhibit six-fold redundancy, and those codons could therefore accommodate 2-3 changes each without changing the coding sequence. These changes could also be incorporated to achieve 60% or lower degrees of sequence homology while retaining enzyme structure.

Creation of deletion mutants. Creation of a deletion mutant as claimed following the teachings of the invention would have taken at most a month. One of skill would have first attempted N-terminal and C-terminal deletions, along with deletions shown as gaps in the described alignment. These experiments could have been done in parallel. As delta-six desaturases are not highly conserved, and the related sequences show deletions, these experiments would have been expected to produce functional enzymes by one of skill.

As the claims are presumed enabled until scientific evidence is provided sufficient to refute enablement, and no such evidence has been provided, lack of enablement has not been established. Caselaw establishes that rejections which merely assert the claims require undue experimentation without evidence do not satisfy the legal standard to establish lack of enablement. Additionally, Applicants have described above how sequences could be obtained meeting all the claim limitations without undue experimentation following the application teachings. Accordingly, the claims stand enabled. Withdrawal of the rejections is respectfully requested.

The rejections of Claims 298, 299, 301-309, 330, 343, 356 and 369

Claims 298, 299, 301-309, 330, 343, 356 and 369 were also rejected under 35 USC 112, second paragraph as indefinite. These rejections are traversed.

The Office Action at page 4 incorrectly stated that Applicants' prior response did not address the rejection in the Office Action of Nov. 14, 2005. The Examiner's attention is directed to pages 15-16 of Applicants' response of May 15, 2006, which addressed both the written description rejection as well as the indefiniteness rejection of these claims.

Applicants respectfully request consideration of their previously submitted arguments. It is submitted that a final Office Action was inappropriate in that Applicants' submitted arguments were not fairly considered.

"The requirement to 'distinctly' claim means that the claim must have a meaning discernible to one of ordinary skill in the art when construed according to correct principles. Only when a claim remains insolubly ambiguous without a discernible meaning after all reasonable attempts at construction must a court declare it indefinite." *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1366, 71 USPQ2d 1081, 1089 (Fed. Cir. 2004).

The Federal Circuit has explained that a claim will not be invalidated for indefiniteness without a severe defect:

[W]e have not held that a claim is indefinite merely because it poses a difficult issue of claim construction. We engage in claim construction every day, and cases frequently present close questions We have not insisted that claims be plain on their face in order to avoid condemnation for indefiniteness; rather, what we have asked is that the claims be amenable to construction, however difficult that task may be. If a claim is insolubly ambiguous, and no narrowing construction can properly be adopted, we have held the claim indefinite. If the meaning of the claim is discernible, even though the task may be formidable and the conclusion may be one over which reasonable persons will disagree, we have held the claim sufficiently clear to avoid invalidity on indefiniteness grounds.

Exxon Research and Eng'g Co. v. United States, 265 F.3d 1371, 1375 (Fed. Cir. 2001) (emphasis added, internal citations omitted).

MPEP 2173.02 reiterates this, stating that a claim term is definite if its meaning is discernible (citing *Bancorp Services, L.L.C. v. Hartford Life Ins. Co.*, 359 F.3d 1367, 1372, 69 USPQ2d 1996, 1999-2000 (Fed. Cir. 2004)). Only if a claim term is insolubly ambiguous after all reasonable efforts at construction can it be declared indefinite.

The Office Action of Nov. 14, 2005 alleged that one of skill would not know what conditions the Applicants would have used for hybridization, and thus this term was indefinite. However, one of skill need only be able to ascertain the conditions that meet the claim limitation for the claims to be sufficiently clear and definite. Applicants have asserted that one of skill could discern the full range of hybridization conditions which meet this claim limitation within at most two weeks. This assertion has not been contradicted.

Applicants are permitted to use relative standards (see MPEP 2173.05(b and g)), and have recited such a standard. Here the standard requires that the hybridization conditions be suitable for selective screening a recombinant library from *Mortierella*, or *M. alpina*, using the complement of SEQ ID NO: 1.

The Office Action of 11/14/2005 alleged that this standard is even more confusing to one of skill, but provided no evidence to support this statement. If the Examiner is relying on personal knowledge, he is requested to provide such a statement in a declaration so that it may be rebutted. The conclusory statement in the Office Action does not meet the standard to establish indefiniteness; no reasonable effort has been made to construe the claim term. One of skill can discern hybridization conditions suitable for selectively screening a library comprising *Mortierella* sequences using the complement of SEQ ID NO: 1.

As the claim language permits one of skill to determine the metes and bounds of protection, claims 298, 299, 301-309, 330, 343, 356 and 369 meet the requirements of 35 USC 112, second paragraph. Withdrawal of these rejections is respectfully requested.

CONCLUSION

Applicants request reconsideration of the claims in view of the above amendments and remarks. A notice of allowance is earnestly solicited. The Examiner is requested to contact the undersigned at (858) 228-7829 prior to a first Office Action.

Respectfully submitted,

/David W. Maher/
David W. Maher
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Exhibit A

MA29 MGTDQG|KTFW- 10 20 30 40 50 60 70
 MAAAP SVRFT|TRAEVNAEALNEGGKDAEAP - FLM|DNKIVYDREHPDHPGSV|LTHV-GKDGTDV 59 67
 MA - - - - - AQIKKYITSDELKNHDKPQGD|WIS|QGKAYDVS DWVKDHPGGSFPLKSJAGQEVTDA 59
 BorD6 ML-TAE-RI - - - - -
 Sy6803D6 MTSTS[KV] - - - - -
 Sp1D6

MA29 FEMYHAFEGAADAIMKKYYGTLVSNELP|FEPPTVFKHTKTRVEGYETDRNIDPKNRPEIWGRYALLFG 129
 FDTHIP-EAAWETLANFYVGDESDRDI - - - - - KNDHAAEV - RKLRTIFGSLGYYDSSKAYAFKVSFNLC 133
 FVAHIP-ASTWKNLDDKF|GYYL-KDY - - - - - SVSEVSKDY RKLVFEFSKMGLYDKK - - - GHIMFATLC 118
 Sy6803D6 - - - - - KFTOKRGFRVLNQRVDIAFEHLQTORDNPSPMYLKTLI[V]L 49
 Sp1D6 - - - - - FGKS1GERKEKLNRVRYNALEAENIS[P]RDNP[P]PMYLKTAI[LA] 50

MA29 SLIASYYAQLFVPPFVERTWLQWVFALIMGFACAQVG_LNP|HDASHFSVTHNNTVWKLLGATHDFNGAS| 199
 IWGL - - STVIAKWGQTST|LANN|LSAALLGL|FWQQCGW-LAHDFLHHQVFDRFWGD|LFGAFLGGVCQGF 200
 MA524 FIAMLFAMS VGVLC|GVLVHLSGC|LMGFLW|QSGW-GHDAGHYMN|SDSRLN[X]NQIFAAACLSGI 187
 BorD6 W|LFSAW - - AFVLFAPVIFPVRLGCMVLA|ALA|AAFSFNV|SHDANHNAYSNPHINRVLGMTYDFVGLSS| 116
 Sy6803D6 WVSAW - - T|FVVF|GPDLWMMKLLGC|V|GFGVSAVGFNI SHDGNHGGSKYQWWNYLSQI[HDAIGVSS| 117
 Sp1D6

FIG. 5A

	220	230	240	250	260	270	280
MA29	YLVWMYQ_HMLGHHPYTNLAGADPDVS			- - - - -	SEPDVRRRIKPN	- QKWFVNHNQHMEV	- - - - - PFLYGC
MA524	SSSMWKDKHINT_HHAAPNVHGEDPDIIDHPLL			- - - - -	WSSHALEMFSODVP	- DEELT - RMWSRFMVLNQTW	256
BorD6	SIGMWKWNHN_AHHIACNSLEYDPLQYIPFLVY			- - - - -	SKFFGSLTSFHYEKR	- LTFDSLRSRFEVSYQHWT	257
Sy6803D6	F_L_WRYR_HNYLHHHTNTNIGHDVIEHG			- - - - -	D_GAVRMSPIE	- - - - - QEHVGILYRF	258
Sp1D6	YL_WKFR_HNVLHHHTNTNIGHDVIEHG			- - - - -	D_ELVRMSPS	- - - - - QEFYI	170
						- - - - - WGLYL	
						- - - - - WFVYP	171
	290	300	310	320	330	340	350
MA29	LIAAF - - [KVR]QD_INLYFVKTNDAIRVNPISTWHTVMFWGKAF			- - - - - FVWYRLIVPLOY	[LPLGKVLLFTV		
MA524	IICFARLSWC[QS]I[FVLPNGQAHKPSGARYP_ISLVEQLS			- - - - - SLAMHW	[LATMFLF_KDPVYNM	322	
BorD6	IMSAARLNMVYVQLSIM[LTK - - - - - RNV[S]			- - - - - YRAQELLGCLVIESIWY	IVY[LY	335	
Sy6803D6	WFLYDVYLNGKGYHDHKIP[PFQPLELASL[- - - - - PLLVSCPNWGGERIMFVIA		315	
Sp1D6	FIPY - - - YWS[ADYQTM[FKRQYHDHEI			- - - - - VFLGLVFG[LPALGFS	[PEV[LGASV]	237	
				- - - - - IFSVAVFL[IPAVGYSPLAEV			
	360	370	380	390	400	410	420
MA29	ADMVSSYVIALTFOANHVEEVQWPLPDE			- - - - - NGLIQKDWAAMQVETQDYAHDSHLWTS	TGSILNYQAVHH		
MA524	SQANICGNILAI[VFSLNHNMPVI - - - - -			- - - - - TGTQI	ITGRDVHPG - LFANWFTGGI	391	
BorD6	SLSMTG_MQQQFSLNHESSSVY - - - - -			- - - - - SKEEAVDMDFFTKQ	NYQIEHH	399	
Sy6803D6	TYMTYGIVVCTIFMLAHVLESTEFLTPDGESGN			- - - - - V[GPKAGNNWIEKQDTGID	QDFQI	377	
Sp1D6	VYMTTHGLVACVFMMLAHVIEPAEFLDPDNL - - H			- - - - - DDEWAI	QIQTIANFAATNNPFPWWFQGGI	307	
				- - - - - HDEWAI	NHQVTHH		
				- - - - - AQVKT	TVDF[APNPNI		
				- - - - - TVDF	INWVGGILNYQITVHH		

FIG. 5B

430 440 450 460 470 480 490

MA29 LFPNVSQHHYPDILAIKNTCSEYKVPYLVKDTFWQAFASHLEHLRVLGLRPKE-----E-----446
MA524 LFPNSMPRHNF SKI QPAVETLCKKMNVRYHT-TGMLEGTAEVFSRLNEVSKAASKMGKAQ-----457
BorD6 LFPKMPRCNLRKISPYVIELCKKKHNLIPNY-ASEISKANEMT[RETRILRINTALQARDITKPLPKNLVWEALHT-----446
Sy6803D6 LFPNICHIHYPQLENIKDVCQEFGVEYKVKPFFKAAIASNYRWLEAMGKAS-----359
Sp1D6 LFPFICHIHYPK[AP][LAEVCE]FGMNYAVHOTFFGAL[ANYSWLKKMSINP]ET-----KAI EQ-----366

FIG. 5C

430 440 450 460 470 480 490

MA29 L FPNVSQHYPDILAIKNTCSEYKVPYLVKDTFWQAFASHLEHLRVGLRPKE-----E-----
MA524 L FPIISMPRHNFNSKIGPAVETLICKKYMVRHT-TGMIEGTAEVFSRLNEVSKAASKMGKAQ
BorD6 L FPKMPRCNLRKISPYIELCKKKHNLIPYN-A-SFISIAANEMTURTLRNTAQLQARDITKPLPKNLVWEALHT
Sy6803D6 L FPNICHIHYPQLENIKDVQEFGVEYKVYPTFKAAIASNYRWLEAMGKAS
Sp1D6 L FPHICHIHYPKRAPILAEVCEFGMNVAYVHQTFEGALAAINYSWLKKMSINPSET-----KAIEQ

FIG. 5C